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Immune Response toward Mycobacterium Tuberculosis Infection

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ABSTRACT

Understanding the human immune response toward Mycobacterium tuberculosis infection is important for controlling its infection. Its transmission through the air consists of "droplets nuclei" containing TB bacilli. After initial infection, the human body will provide diverse immune responses and will determine different clinico-histopathologic finding. This response starts from innate immunity that consists of phagocytosis by distal alveolar macrophages or nasal microfold cells, then will be continued by dendritic cells to be transferred to mediastinal lymph nodes to induced adaptive immune responses. This response is mediated by cells through IFN- γ signaling which will enhance phagocytosis. If this response is effective, there will be a latent infection with an initial histopathological finding of caseosa granulomas and predominantly followed by chronic granulomas. In a few cases, it can be reactivated via the IL-10 activation pathway and exogenous factors, it will induce a great adaptive immune reaction and provide more severe clinico-histopathological manifestation. The existence of the human body's immune response to Mycobacterium tuberculosis, etiher innate or adaptive immunity will determine the clinical course and pathology that will occur.

Keywords: Adaptive immunity; innate immunity; mycobacterium tuberculosis; tuberculosis

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Introduction

Mycobacterium tuberculosis (MTb) was first discovered by German scientist Robert Koch as a cause of tuberculosis (TB) in 1882. At that time, tuberculosis was the cause of death for 25% of people living in New York, Massachusetts, and Europe.[1] Not yet known surely, the early history of these bacteria spread among humans. It is known that in the year 5000 BC found a spine deformity which is typically caused by MTb bacteria in Peru and Egypt. The domestication process of cattle facilitates close contact between humans and cattle carrying *M. bovis*, a strain of tuberculosis in cattle, which is thought to have evolved. These bacteria then spread into an epidemic in the early 17th century where there was an increase in urbanization in Western Europe, so it was known as the "*Great White Plague*".[2]

According to the WHO report, about a quarter of the world's population has latent TB, i.e. people infected with MTb but show no symptoms of the disease. 10 million of them, in 2018 had tuberculosis with a composition of 5.7 million in the male population, 3.2 million in the female population, and 1.1 million in the children's population. Then in the same year, 1.5 million people died due to TB (including 251,000 people with HIV) which made this disease the top 10 causes of death.[3] In Indonesia, the number of new cases in 2017 was 420,994 in which the proportion of male patients is 1.4 times greater than female patients. In 2013-2014, Tuberculosis Prevalence Survey found a total confirmation case in Indonesia was 759 per 100,000 and an Acid Fast Staining (AFS) confirmation case in Indonesia was 257 per 100,000 population aged 15 years and over. Of all cases handled in 2017, 2.5% of people died.[4]

MTb infection is obtained from inhalation of infectious aerosol particles in the air that spread from person to person in close contact.[5] This was first explained by Wells in 1930, where he discovered that the MTb that came out of a patient's cough was in a 1-micron droplet in the air, called a 'droplets nuclei'. These droplets nuclei have a unique characteristic because it can survive in the air until finally inhaled by others and into his lungs. The more droplets of the nucleus that are inhaled, the almost as many lesions arise in the lungs. Infection can occur, even by a single bacillus tubercle.[2]

People infected with MTb have three possibilities, namely spontaneous recovery, latent infection or Latent TB Infection (LTBI), and active TB.[2] People who recover spontaneously can be due to three possibilities, namely due to inadequate dose of infectious, adequate innate immune response, or localized immune response.[6] This can be more clearly seen in Figure 1.

People infected with MTb are proven by tuberculin skin tests and positive interferon-gamma release assay (IGRA), but do not show clinical symptoms referred to as LTBI.[7] Whereas 5-10% of LTBI will develop active TB, where HIV patient, cancer patient, patients taking immunosuppressive drugs, and other immunocompromised patients have a high risk of getting into this group.[5]

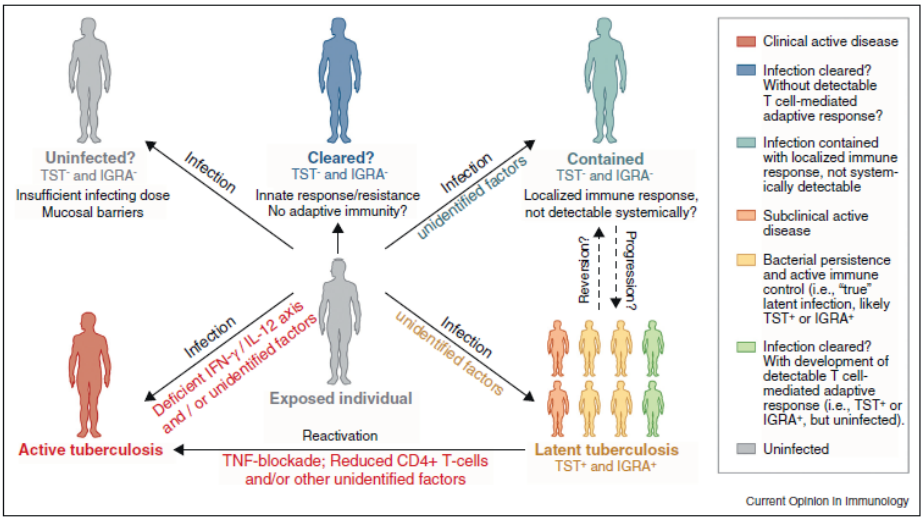

Figure 1. Three clinical possibilites of people infected with MTb.[6]

Various forms of MTb infections as mentioned above depend on the body's immune response against it. Several components of the immune system that have been confirmed to include are CD4+T cells, IL-12 cytokines, Interferon-gamma (IFN-γ), and tumor necrosis factor (TNF). Although there are also several other components of immunity that play an important role.[6] The role of the immune response between the LTBI phases to be active makes this very important to be discussed and can be material for the development of controlling MTb infection and its vaccination.[8] Therefore, this article will discuss the morphology and virulence of MTb and how the human body's immune response to the infection.

Research Methods

This article uses narrative literature review approaches based on the literature on PubMed and Crossref in the last 10 years ago, except for historical article, the guideline, and the textbook. The terms that are used for searching literature are “adaptive immunity”, ‘innate immunity”, “Mycobacterium tuberculosis”, and “tuberculosis infection”.

Morphology and Virulence of MTb

MTb is gram-positive mycobacteria which is aerobic-microaerophilic, not sporous, and members of the Actinomycete family bacteria.[9] These bacteria have a characteristic that is resistant to acidic alcohol staining which is characterized by not changing its color by gram staining. Therefore, these bacteria are often referred to as Acid Fast Basil (AFB) bacteria. Although, this character is not only possessed by MTb but also by Nocardia spp. and other parasites.[2] The wall structure of these bacteria which determines the antigenic site can be seen in Figure 2.

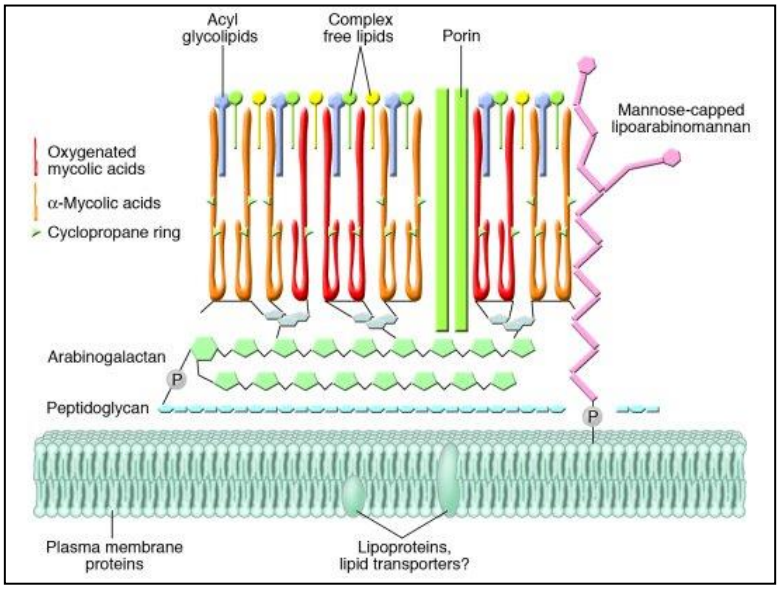

Figure 2. Wall structure of mycobacterium tuberculosis that determine the antigenic features.[10]

Mycobacterium has relatively slow growth. Most bacteria have a proliferation time of about 20 minutes in vitro, whereas mycobacteria can reach 18-24 hours. This is what influences the length of time of culture examination to establish the diagnosis of this disease.[2]

There are more than 20 species of mycobacterium that can cause disease in humans, but the most important is MTb due to many of its effects as pathogens in humans.[2] These bacteria are obligate intracellular parasites. Some parasites that can also cause MTb-like infections are *M. bovis, M. bovis BCG* (vaccine strain) subspecies, *M. microti*, and *M. afircanum.*[11]

MTb has a standard strain, i.e. the H37Rv genome consisting of 4411 kb with 65% GC content and a minimum of 3924 open reading frames (ORFs) which can be predicted to potentially encode a protein.[12] It is possible to have several other strains that have different virulence. The CDC-1551 strain, which was the cause of the TB outbreak in Kentucky and Tennessee in 1994-1996, produced a faster and more aggressive immune response than the standard H37Rv strain. The probability of LTBI form of the CDC-1551 strain is relatively higher, where among of 429 people infected with MTb, there are 311 people (around 72%) who have positive skin tuberculin tests.[13] In experimental animals, this CD-1551 strain has a higher replication ability than the standard strains similar to H37Rv. Strain CDC-1551 can induce granulomatous differentiation and high cytokine levels in the lungs at an earlier time than other strains.[14]

Immune Response toward MTb Infection

The continuation of MTb infection in the human body depends on the initial response when they enter the human body in the form of droplets nuclei. The most determining factor for the presence of MTb in a dropletnuclei is the size of the droplet itself.

There are three types of droplet sizes, namely small droplets, medium droplets, and large droplets. Small droplets do not contain MTb. Medium droplets with size 1-5 µm contain MTb bacteria and are easily inhaled up to the alveoli because they can survive in the air. Whereas large droplets quickly fall to the ground before being evaporated.[15] The degree of infection depends on how many droplets nuclei enter the lungs.[2,6] Patients with symptomatic active TB have millions of MTb bacteria in their bodies. They secrete about 3,000 droplets nuclei while coughing and more than 10,000 droplets nuclei while sneezing.[15]

The general paradigm states that the immune system that first recognizes MTb is macrophages and dendritic cells that patrol the terminal alveoli.[16] However, other theories state that microfold cells (M-cells) in the nasal mucosal epithelium are involved as first immunity against MTb. M-cells are part of the Mucosal Associated Lymphoid Tissue (MALT). When the MTb enters the M-cell, there will be a rapid translocation of the germ to another M-cell, until finally it is disseminated to the nearest lymphonodi (Figure 3).[17] However, this theory is not fully understanding.

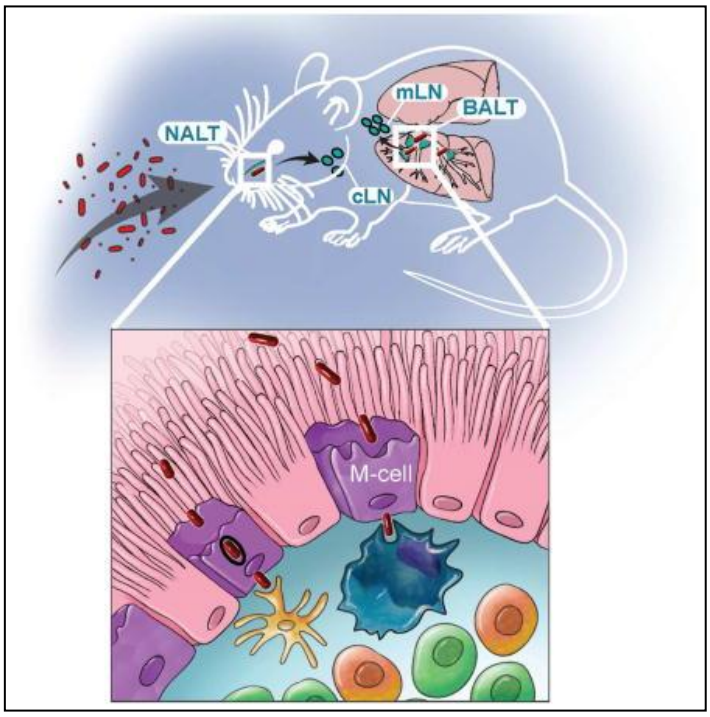

Figure 3. M-cells role in initiation of MTb infection in murine model.[17]

This figure shows M-Cells as part of NALT and BALT has a role in the initiation of MTb infection via rapid translocation before introduced to macrophage or dendritic cells. After that, the MTb can disseminate to draining lymph nodes, including cervical lymph nodes or mediastinal lymph nodes to induced adaptive immunity cascade.
BALT: Bronchial Associated Lymphoid Tissue; cLN: cervical Lymph Nodes; M-cell: microfold cells; mLN: mediastinal Lymph Nodes; NALT: Nasal Associated Lymphoid Tissue.

Based on the general paradigm, after the MTb enters the macrophage, a response will occur depending on the body's immune status. If the immune status is good, then macrophages will phagocytosis and kill the MTb. However, if it is not successfully phagocyted, the bacteria will rapidly proliferate with dendritic cells and alveolar macrophages and produce signals in the form of cytokines IL-1α, IL-1β, and other proinflammatory cytokines.[16]

This response is mediated by pattern recognition receptors (PRRs) expressed by macrophages, dendritic cells, neutrophils, and Natural Killer (NK) cells when recognizing pathogen-associated molecular patterns (PAMPs) antigens from MTb bacteria. There are three groups of receptors responsible for this innate immune response, namely the Toll-Like Receptor (TLR), Nod-Like Receptor (NLR), and C-type Lectin Receptor (CLR). Activation of receptors by MTb bacteria will trigger various cellular responses, ranging from phagocytosis, autophagy, apoptosis, and inflammatory reactions.[18,19]

MTb cell walls that contain mannose-caped lipoarabinomannan will induce the expression of Peroxisome Proliferator-Activated Receptor ϒ (PPARϒ) through the mannose-receptor dependent pathway. When activated, PPARϒ will increase the expression of IL-8 and cyclooxygenase-2. On the other side, MAPK-p38 mediates the activation of cytosolic phospholipase A2 to produce ligands for PPARϒ. The presence of defects from PPARϒ from macrophages will increase the production of TNF and control the intracellular growth of MTb.[20]

Also, Toll-Like Receptors (TLRs) help the entry of MTb into macrophages and dendritic cells and will induce an intracellular cascade signaling to produce cytokines. During this innate immune response, MTb bacteria proliferate together with human body cells and induce cell death through the secretion of the type VII ESX1 virulence factor system. The new mechanism will delay the adaptive immune response.[21]

This barrier of adaptive immune response is unique because it can occur for a long time between 2-12 weeks after the initial infection.[22] If the stage has passed, the dendritic cells will carry the MTb bacteria to the mediastinal lymph nodes, which is the place where the antigen-presenting cells (APCs) will activate T cells. These bacilli bacteria will then be processed into Major Histocompatibility Complex (MHC) class II molecules, which will then trigger activation of T helper 1 (Th1) cells to secrete IFN-ϒ to the lungs. Production of IFN- ϒ can negatively regulate the production of T helper 2 (Th2) cytokines (IL-4, IL-5, and IL-13) and the participation of suppressor of cytokine signaling (SOCS)-1 that have been reported contribute to the severity of MTb infection. When the adaptive immune response is active, both the effector of CD4+ cells and CD8+ cells will be induced. During this period, the MTb bacteria can mutate to change its surface receptors and continuously trigger the production of cytokines such as IFN-ϒ.[16,23,24]

After the continuous production of cytokines, T cells limit the mobility of macrophages and activate their function.[23] At this stage, "granuloma immune" is formed which in histopathological features is composed of macrophages, neutrophils, monocytes, dendritic cells, and T cells. Granuloma formed may be to limit the growth area of MTb.[5]

For a long time, if this MTb did not pass this granuloma, chronic granulomas would form which in histopathological features is composed of foamy and epithelioid macrophages which are covered by fibrotic tissue. MTb bacteria can escape from this immune granuloma through the activation of IL-10 which will suppress the T-cell activity.[5]

There is a delay between MTb infection and T cell response. MTb bacteria are in a dormant phase clinically called Latent TB Infection (LTBI), where bacilli are controlled for growth through adaptive immunity by being held in granulomas, or by nitric oxide (NO) in rats or antimicrobial peptides in humans.[22,25] This latent infection is characterized by a healed granuloma, which on the histopathological picture has a central calcification and is surrounded by fibrotic capsules and no bacilli are detected in it.[26]

Under certain conditions, these bacteria in dormant status can reactivate through several exogenous factors.[5] There is a protein secretion that resembles a Resuscitation-promoting factor (Rpf) which will reactivate the MTb dormant form to proliferate.[21] Moreover, there are the toxin-antitoxin (TA) gene or plasmid factor encoded by the MTb to change the status of the bacteria from latent to active phase again by producing a toxin that can kill these cells. The exact mechanism of reactivation is still unknown and needs to be further investigated.[25]

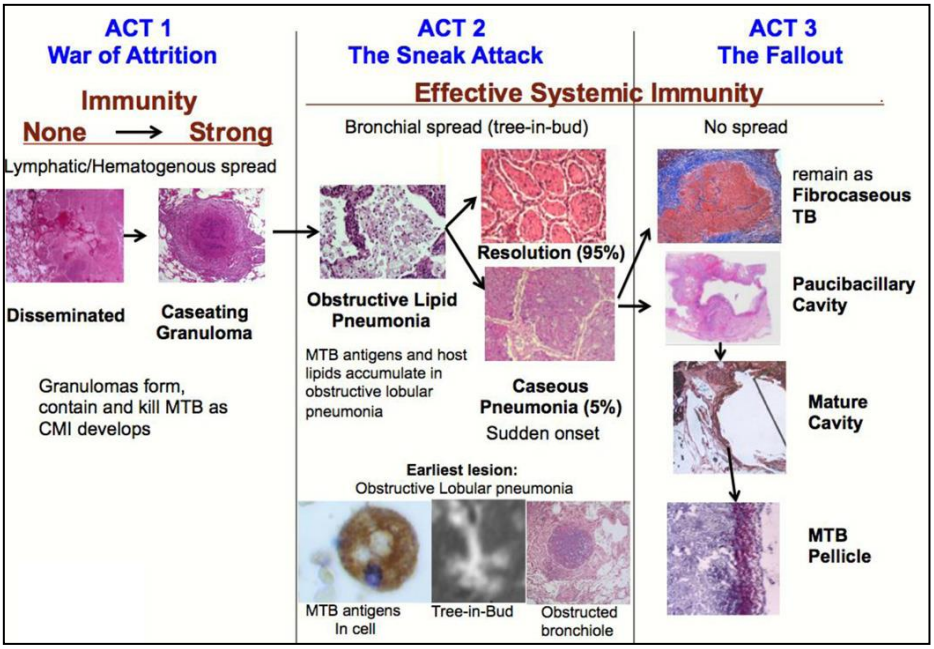

Figure 4. Histopathologic concept features of "*Three-Act Play*" in pathogenesis of MTb infection.[27]
This picture shows the new histopathological concept of the "three-act play" in the pathogenesis of MTb infection. ACT 1 is a war of attrition where there will be a war between macrophage cells and MTb germs that can be stopped if CMI is formed. This is marked by the formation of granulomas. ACT 2 is a condition in which a systemic immune response has been effective where a dominant histopathological picture of obstructive lobular pneumonia appears to be effective in inhibiting MTb growth and only a few (5%) develops into caseous pneumonia. ACT 3 is an advanced disease of caseosa pneumonia, where fibrocaseous TB or TB cavity can occur.
ACT: Action; CMI: Cell Mediated Immunity; MTB: Mycobacterium tuberculosis

Under adaptive immune conditions, MTb can have various clinical manifestations depending on where they proliferate.[26] Proliferation can occur in the spine, pelvis, and digestive tract. However, it is 85% likely to occur in the lungs.[22] In the lungs, clinical manifestations that can occur include respiratory symptoms (cough more than 3 weeks, hemoptoe, shortness of breath, and chest pain) as well as systemic symptoms such as fever, malaise, night sweating, anorexia, and weight loss. It can also be seen as fibroinfiltrates and pleural effusions on the X-ray examination. These symptoms will appear faintly in elderly patients.[22,26]

The histopathological picture of the immune response to MTb is summarized in the "Three-Act Play" model as shown in Figure 4. Action 1 is a "War of attrition" in which caseosa granulomas form from primary TB as a result of macrophage activity against MTb bacteria before and after mediated by adaptive immunity. Action 2 is the "The Sneak attack" where post-primary bronchogenic TB occurs which ends in 95% improving and 5% forming caseosa pneumonia. Action 3 is "The Fallout" in which further evolution of necrotic caseosa from pneumonia forms cavity or fibrosis with granulomatous inflammation.[27]

Animal Model to Study Interaction between Immune System and MTb

Several animals have been used to research the immune response to MTb. Some of them are mice, pigs, rabbits, and monkeys (macaque).[25] Mice and macaque monkeys are the most commonly used. The use of rats saves more money and can resemble the characteristics of MTb infection, pathogenesis, and its therapeutic response in humans. However, this mouse model cannot resemble the picture of latent MTb infection in humans as can be described by macaque monkeys.[5] However, translational studies using these experimental animals must be carefully translated into the human context because of its complexity.

Immune Response to High Pathogenic MTb

Toll-Like Receptors (TLRs) will help the entry of MTb bacteria into macrophages and dendritic cells and will induce an intracellular cascade of signals to produce cytokines. During this innate immune response, MTb bacteria proliferate together with human body cells and induce cell death through the secretion of the type VII ESX-1 virulence factor system. This virulence factor will delay the adaptive immune response. Barriers to this adaptive immune response are unique because they can occur for quite a long time between 2-12 weeks after infection.[21,22]

Immune Response to MTb Drug Resistance Strain

Antigenic mutations from the surface of the MTb wall occur at the stage of the adaptive immune response.[16] The cell wall complex of the MTb will inhibit drug penetration into the bacteria and trigger the dysregulation mechanism of the immune response. MTb adapts physiologically to various immune responses of the human body until it enters the dormant phase. In this phase occurs immunity to antibiotics whose mechanism of action suppresses the proliferation of MTb.

Moreover, there is an efflux system mechanism that can mitigate the efficacy of the drug by reducing its intracellular concentration. A change in the profile of the mutated MTb bacteria will create a heterogeneous population of bacteria in the body which will complicate the treatment process.[28]

Conclusion and Future Directions

MTb infection in humans is still an important health problem in the world. The existence of the body's immune response to germs will determine the clinical course and pathology that will occur. The immune response starts from innate immunity in the form of phagocytosis by distal alveolar macrophages or recognition by M cells in Nasal Associated Lymphoid Tissue, then will be followed by dendritic cells to be carried to mediastinal lymph nodes to induce an adaptive immune response. This adaptive immune response is mediated by Th cells through IFN- γ signaling with effector CD4+T cells and CD8+T cells which will increase the phagocytic ability of alveolar macrophages against MTb bacteria. If this mechanism is effective, there will be a latent infection or so-called Latent TB Infection (LTBI) with an initial histopathological picture of caseosa granuloma. The majority of caseosa granulomas are effective in suppressing the growth of MTb germs so that at an advanced stage they will form chronic granulomas and heal. In a few cases, dormant MTb bacteria can reactivate via the IL-10 activation pathway, the Rpf gene, and the TA gene. When active again, the person with immunocompetent status will give a great adaptive immune reaction and will provide a clinical picture according to the location where the MTb proliferates. The majority of cases occur in the lungs, with histopathological features in the form of TB fibrocaseosa or cavity. This immune mechanism is still not fully understood. So, it is important to carry out further research, especially in the initial pathway for MTb bacteria to interact with the immune system, immune factors that affect the transition from innate immunity to adaptive immunity, and factors that influence the change from LTBI to active TB, or so-called post TB primary.

Conflict of Interest

There is no conflict of interest while publish this article.

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